DERIVATIVES OF PIPERAZINE IV

By

W. T. FORSEE, JR.

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REVIEW OF THE LITERATURE

Subjects dealing with the reactions between aldehydes and amines occupy a considerable portion of chemical literatures. Piperazine is a secondary amine and shows reactions characteristic of this particular type of compound. Therefore characteristic reactions which take place between aldehydes and amines as a class should apply to piperazine.

A thorough search of the literature reveals very little published work on the reactions between piperazine and aldehydes and this small amount of published work is somewhat contradictory. Before attempting an investigation of the reactions between aldehydes and piperazine, the literature was searched in order to ascertain the types of reaction which take place between aldehydes and amines, particularly secondary amines. Only a representative portion of the large amount of available material on the subject of aldehyde amine reactions will be covered. The review is divided into the following topics: condensations involving the carbonyl group, condensations involving an active hydrogen and alkylation of amines by means of aldehydes.

Condensations Involving the Carbonyl Group

Aromatic aldehydes condense with aniline with the formation of benzylidene anilines[1].

$$C_6H_5CHO + H_2N\text{-}C_6H_5 \longrightarrow C_6H_5\text{-}CH{=}N\text{-}C_6H_5 + H_2O$$

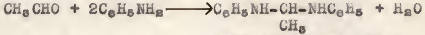
Condensation products of this type are called Schiff bases. They can also be obtained with fatty aldehydes, but they polymerize readily[2]. According to Dimroth and Zoeppritz[3], the first reaction consists in the addition of the amine to the carbonyl group of the aldehyde and subsequent removal of a molecule of water.

$$C_6H_5CHO + H_2N\text{-}C_6H_5 \longrightarrow C_6H_5CH(OH)NH\text{-}C_6H_5$$

$$C_6H_5CH(OH)NH\text{-}C_6H_5 \longrightarrow C_6H_5CH{=}N\text{-}C_6H_5 + H_2O$$

With few exceptions it has been found impossible to isolate the intermediate additive products. Dimroth and Zoeppritz isolated six of these intermediate products in the form of their hydrochlorides. Claisen[4] reacted benzaldehyde with β-naphthylamine and obtained benzal-β-naphthylamine.

Aliphatic aldehydes react with primary bases, with the elimination of water[5], thus

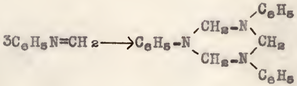


$$CH_3CHO + 2C_6H_5NH_2 \longrightarrow C_6H_5NH\text{-}\underset{CH_3}{CH}\text{-}NHC_6H_5 + H_2O$$

(ethylidene aniline)

Aberhardt and Welter[7] obtained methylenediphenyldiamine by treating aniline with formaldehyde in alcoholic potassium hydroxide solution at 100° C. This product yielded formaldehyde when boiled with dilute H_2SO_4. Analagous reactions were obtained with o- and p-toluidines. An azo-methine may also be obtained from aniline and formaldehyde[8]. This compound polymerizes, depending on the temperature.

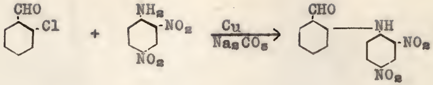
$$C_6H_5NH_2 + HCHO \longrightarrow C_6H_5N{=}CH_2 + H_2O$$



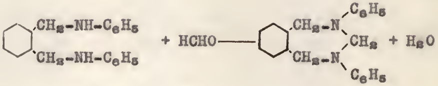
Strong hydrochloric acid causes decomposition into the original aldehyde and amine. Formaldehyde forms a Schiff base, formaldoxime, with hydroxylamine[9].

When formaldehyde acts on methylaniline or its aliphatic homologues in neutral or alkaline solution, condensation readily occurs with the formation of derivatives of methylenediamine[10]. In the case of methyl-o-toluidine the reaction is more sluggish and still more so with p-toluidine.

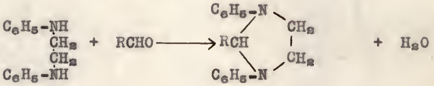
Ortho- chlorobenzaldehyde gives azo-methine derivatives with aniline and chlorine substituted anilines[11]. However, this aldehyde does not always form this type of compound with very weak bases such as 2,4-dinitroaniline[12], e.g.



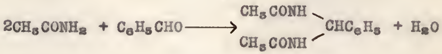
Chloral and two molecules of aniline lose water with the formation of trichlorethylidine diphenylamine[13]. Aldehydes react with diamines with the characteristic splitting out of water[14].



Diethylene aniline with an aldehyde yields a compound with a pentatomic ring[15], e.g.



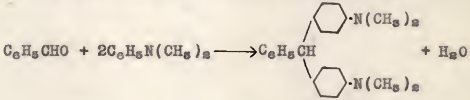
Roth[16] found that acid amides condensed with aldehydes in an analogous manner.



$$2CH_3CONH_2 + C_6H_5CHO \longrightarrow \begin{matrix} CH_3CONH \\ CH_3CONH \end{matrix}\!\!> CHC_6H_5 + H_2O$$

Condensations Involving an Active Hydrogen

Two molecules of a tertiary aromatic amine[1] condense with one molecule of an aldehyde with the splitting out of water between the oxygen of the carbonyl group and the hydrogens para to the amino groups.

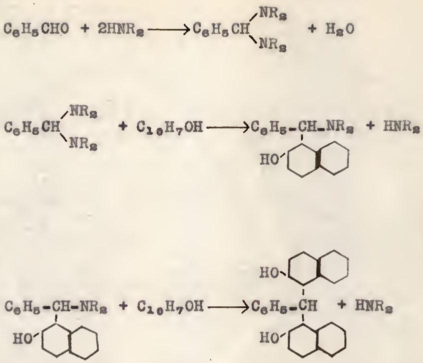


Chloral hydrate undergoes an aldol condensation with secondary[17] and tertiary[18] aromatic amines. These condensations involve the hydrogen para to the amino group.

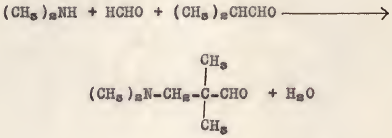
$$C_6H_5NHCH_3 + CCl_3CH(OH)_2 \xrightarrow[\text{at } 40 - 50°]{\text{stand 24 hrs.}}$$

$$CCl_3CH(OH)\text{-}C_6H_4NHCH_3 + H_2O$$

Littman and Brode[19] obtained 1-(α-1-piperidylbenzal)-2-naphthol by slowly adding piperidine to molar quantities of β-naphthol and benzaldehyde dissolved in absolute alcohol. This product yielded benzal-di-β-naphthol by heating with additional β-naphthol in benzene solution. The following equations explain the process of the reaction.



Secondary amines may be condensed with formaldehyde and another compound containing an active hydrogen. Water is formed, the oxygen coming from the formaldehyde and the hydrogens from the amine and active hydrogen. The following reaction[20] will suffice to illustrate this type of synthesis.



$$(CH_3)_2NH + HCHO + (CH_3)_2CHCHO \longrightarrow (CH_3)_2N\text{-}CH_2\text{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}\text{-}CHO + H_2O$$

Alkylation

Alkylation of an amine takes place when an aldehyde reacts with an amine in the presence of a reducing agent. The reducing agents generally used are zinc and hydrochloric or sulfuric acid and formic acid. Other methods make use of electrolytic and catalytic reductions.

Methylation[21,22] takes place when the hydrochloride of the base is heated to 120 - 160° C. under pressure with formaldehyde. The aldehyde acts as its own reducing agent, being partly oxidized to CO_2 and partly reduced to CH_3OH. The same reaction takes place when one subjects NH_3 or its salt to the action of formaldehyde at elevated temperatures.

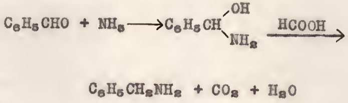
$$2NH_3 + 3HCHO \longrightarrow 2H_2NCH_3 + CO_2 + H_2O$$

$$2NH_3 + 6HCHO \longrightarrow 2HN(CH_3)_2 + 2CO_2 + 2H_2O$$

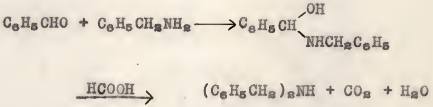
$$2NH_3 + 9HCHO \longrightarrow 2N(CH_3)_3 + 3CO_2 + 3H_2O$$

By this method, ethylamine gave dimethyl ethylamine, benzylamine gave dimethyl benzylamine, ethylenediamine gave tetramethyl ethylenediamine, piperidine gave methylpiperidine and piperazine gave dimethylpiperazine.

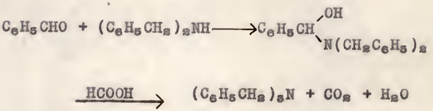
Wallach[25] has done considerable work on the alkylation of amines and ammonia. Aldehydes and ketones were reacted with ammonium formate and the formic acid salts of amines in the presence of formic acid. Benzaldehyde with ammonium formate yields tribenzylamine.



$$C_6H_5CHO + NH_3 \longrightarrow C_6H_5CH\begin{matrix}OH\\NH_2\end{matrix} \xrightarrow{HCOOH} C_6H_5CH_2NH_2 + CO_2 + H_2O$$

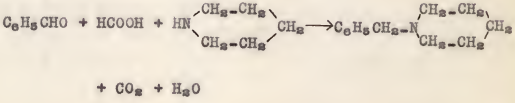


$$C_6H_5CHO + C_6H_5CH_2NH_2 \longrightarrow C_6H_5CH\begin{matrix}OH\\NHCH_2C_6H_5\end{matrix} \xrightarrow{HCOOH} (C_6H_5CH_2)_2NH + CO_2 + H_2O$$



$$C_6H_5CHO + (C_6H_5CH_2)_2NH \longrightarrow C_6H_5CH\begin{matrix}OH\\N(CH_2C_6H_5)_2\end{matrix} \xrightarrow{HCOOH} (C_6H_5CH_2)_3N + CO_2 + H_2O$$

Benzylpiperidine formate was obtained by heating piperidine and benzaldehyde in formic acid. Subsequent treatment with alkali yielded the free base, benzylpiperidine.

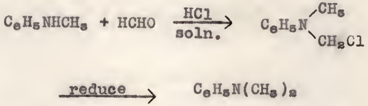


$$C_6H_5CHO + HCOOH + HN\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}CH_2 \longrightarrow C_6H_5CH_2-N\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}CH_2 + CO_2 + H_2O$$

Clark, Gillespie and Weisshaus[24] found that simple aliphatic amines were smoothly methylated to the corresponding tertiary amines by warming in formic acid solution with formaldehyde.

Using tin and hydrochloric acid as the reducing agent, Goldschmidt[25] prepared dimethylaniline from the condensation product of formaldehyde and aniline.

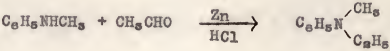
$$C_6H_5NH_2 + HCHO \longrightarrow C_6H_5N{=}CH_2 \xrightarrow[HCl]{Sn} C_6H_5NHCH_3$$



$$C_6H_5NHCH_3 + HCHO \xrightarrow[soln.]{HCl} C_6H_5N\begin{matrix} CH_3 \\ CH_2Cl \end{matrix}$$

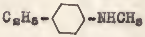
$$\xrightarrow{reduce} C_6H_5N(CH_3)_2$$

Wagner[26], in carrying out research on the alklation of secondary aromatic amines, obtained two types of products depending on the method used. If methylaniline were reacted with acetaldehyde in the presence of hydrochloric acid and zinc, methylethyl aniline was obtained.

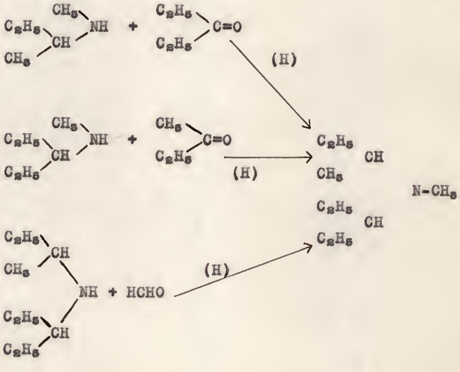


$$C_6H_5NHCH_3 + CH_3CHO \xrightarrow[HCl]{Zn} C_6H_5N\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}$$

By this method, dimethyl, methyl ethyl, methyl n-propyl, methyl n-butyl and methyl isoamyl anilines were prepared from methyl-aniline and the appropriate aldehyde. However, if the aldehyde and amine were condensed in hydrochloric acid solution and the resulting condensation product reduced, the alkyl group was found attached to the carbon para to the amino group.



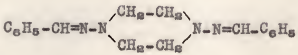
Brand[27] obtained benzylaniline by electrolytic reduction of benzylidene aniline. Skita and others[28,29] have done a large amount of work on the alkylation of secondary amines with aldehydes and ketones by catalytic reduction.



They carried out a large number of these reactions. As a catalyst, they used a solution containing 6 cc. of a 10% solution of chloroplatinous acid and 10 cc. of gum arabic.

Piperazine Compounds

In 1891 Schmidt and Wichmann[30] reacted piperazine with benzaldehyde. Dry piperazine was mixed with benzaldehyde and, after a while, the hardened mass was heated on a water bath. After washing with alcohol there was obtained a white amorphous substance almost insoluble in all solvents. It had a melting point of 246 - 247° C. and they assigned the formula, $C_4H_8N_2 \cdot CHC_6H_5$, benzylidene piperazine. These same workers also obtained an azo methine compound, 1,4-dibenzalaminopiperazine, by the condensation of 1,4-diaminopiperazine and benzaldehyde.



$$C_6H_5-CH=N-N\begin{matrix}/CH_2-CH_2\backslash\\ \backslash CH_2-CH_2/\end{matrix}N-N=CH-C_6H_5$$

Six years later, Herz[31] studied the action of piperazine on formaldehyde and benzaldehyde. He heated piperazine and excess benzaldehyde in a sealed tube at 60° C. A solid compound was obtained which was white after being washed with acetone. It turned yellow in a desiccator and had an odor like that of bitter almond oil. Decomposition had occurred, which was shown by its analysis and molecular weight determination. No formula was proposed. On heating excess 40% formaldehyde solution with piperazine in a sealed tube at

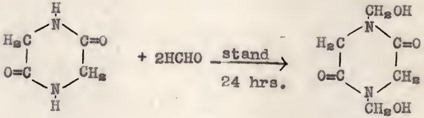
70° C. there was obtained a pale green liquid. The water was evaporated off at 70° C. and there remained a pale green mass which became white on further drying at 70° C. It became brown at 170° C. and decomposed with charring at 225° C. It was not entirely pure since no solvent for recrystallization could be found. Analysis, according to Herz, gave the formula $C_4H_{10}N_2\ 2CH_2O$. This would indicate an aldol type of condensation.

Eschweiler[21] obtained dimethyl piperazine by heating piperazine and formaldehyde to 120 - 160° C. in a closed flask. The published report gave no properties, constants, analyses or formula for the compound. Scott[22], in the process of the preparation of rubber accelerators, condensed piperazine with several aldehydes. Other than a simple statement that this had been done, there was no other information as to the formula and properties of these piperazine condensation products. However, using piperidine and formaldehyde as an example, Scott did indicate that the reaction split out water between the carbonyl group and the two hydrogens attached to two amino groups.

$$\text{piperidine + paraformaldehyde} \longrightarrow C_5H_{10}N\text{-}CH_2\text{-}NC_5H_{10}$$

These products were condensed with carbon disulfide in order to obtain the desired rubber accelerators.

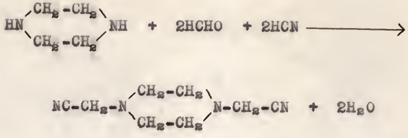
Cherbuliez and Feer[33] obtained 2,5-diketo-N,N′-hydroxymethyl piperazine by treating 2,5-diketopiperazine with excess formaldehyde.



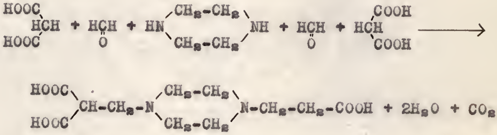
This would seem to substantiate the results reported by Herz[31].

However, Prelog and Blazik[34] obtained N-bis-(N′-phenyl-piperazyl)-methane by shaking N-monophenylpiperazine with a 40% formaldehyde solution. This compound was recrystallized from a freezing mixture of benzene and petroleum ether and the melting point reported as 133° C.

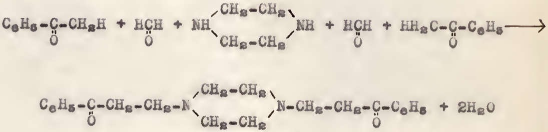
Condensation products have been made from piperazine and formaldehyde with some other substance containing an active hydrogen. 1,4-piperazine-diacetonitrile[35] has been made from piperazine, formaldehyde and hydrogen cynnide.



Mannich and Ganz[26] prepared piperazine-N-β-propionic-N$'$-β'-isosuccinic acid by condensing malonic acid, formaldehyde and piperazine.



Mannich and Lammering[27] synthesized β-keto bases from fatty aromatic ketones, formaldehyde and secondary amines. By this method they prepared 1,4-di-(β-benzoylethyl)-piperazine.



The preparation of alkyl piperazines by the alkylation of piperazine and N-monophenylpiperazine resulted in the synthesis of several compounds which had previously been prepared by other methods. Since they have not been covered in the previous pages of this dissertation, reference is here made to these compounds.

Ladenburg[39] prepared diethylenedimethyldiamine from piperazine and potassium methylsulfate. Schmidt and Wichman[40] also prepared this compound and reported its boiling point as 153 - 158° C. These same authors prepared the dihydrochloride of this compound, reporting a melting point of 247 - 250° C. Meyer and Jacobsen[41] report a boiling point of 131 - 132° C. for this dimethyl piperazine compound. The corresponding product from formaldehyde obtained in this investigation boiled at 130 - 135° C. and its dihydrochloride melted at 263° C.

Schmidt and Wichmann[40] prepared diethylenediethyldiamine from ethylenedibromide and ethylamine. The reported boiling point is 165° C. and the dihydrochloride melted at 277° C. Hoffmann[42] synthesized diethylenediethyldiamine from piperazine and ethyl iodide and reported its boiling point as 185° C. The product obtained in this investigation from acetaldehyde boiled at 174 - 177° C. and its hydrochloride melted at 277° C.

Prelog and Stephan[48] prepared N-methyl-N$'$-phenylpiperazine from N-methyl-bis-(β-bromethyl)-amine and aniline. The base was distilled at 140 - 142° C. at 3 mm. These investigators also prepared N-ethyl-N$'$-phenylpiperazine by an analogous reaction. The boiling point of this compound was reported as 157 - 158° C. at 10 mm.

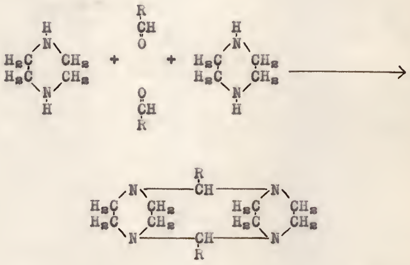
INTRODUCTION AND STATEMENT OF PROBLEM

Contradictions in the preceding review are evident with respect to piperazine aldehyde reactions as reported. Two investigators, one using piperazine[32] and the other using N-monophenyl piperazine[34] with formaldehyde, reported compounds containing a methylene carbon attached to two nitrogen atoms. On the other hand, two investigators, one using piperazine[31] and the other using 2,5-diketopiperazine[33] with formaldehyde, reported respectively compounds containing one mole of piperazine combined with two moles of formaldehyde and a N,N′-hydroxymethyl compound. Still another investigator reports a N,N′-dimethylpiperazine[21] from piperazine and formaldehyde. The preceding discussion of aldehyde amine reactions would indicate that the first mentioned type of compound should be formed. Only one investigator's results[30] warranted assigning a formula when piperazine was condensed with an aromatic aldehyde. A benzylidene compound was obtained from piperazine and benzaldehyde. This type of reaction, the straight condensation of piperazine and aldehydes forms the basis for part of this investigation.

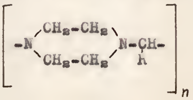
The condensation of amines and aldehydes in an acid medium and in the presence of a reducing agent forms another interesting phase of aldehyde amine reactions. This type of synthesis results in the alkylation of amines and forms the basis for another part of this investigation, that is, alkylation of piperazine and piperazine derivatives by means of aldehydes.

DISCUSSION OF PROBLEM AND RESULTS

The small amount of experimental evidence has failed to establish a basis for predicting the type of compound expected when aldehydes condense with piperazine. However, experimental evidence gathered from the condensation of aldehydes and amines in general seems to indicate that piperazine and aldehydes should condense in the ratio of one mole of piperazine to one mole of aldehyde. This reaction could be most simply represented as follows:



However, a polymer of this compound could be formed.



In this investigation, piperazine was condensed with formaldehyde, acetaldehyde, butyraldehyde, benzaldehyde, salicylaldehyde, p-tolylaldehyde, o-chlorobenzaldehyde and anisaldehyde. In every case except with acetaldehyde and butyraldehyde, analysis indicated a compound of the above structure. Benzaldehyde and piperazine gave a compound whose analysis indicated it to be benzylidene piperazine. Its melting point was 270° C., twenty four degrees higher than that reported by Schmidt and Wichmann[36]. In order to confirm this structure, piperazine was reacted with benzalchloride* in the presence of a base. The resulting compound had a melting point of 265° C. Analysis, physical constants and mixed melting points showed it to be the same compound as the one obtained from benzaldehyde and piperazine. The melting point of a mixture of the two was 265° C. Benzylidenepiperazine is insoluble in all solvents, therefore a molecular weight determination was not attempted. Benzylidenepiperazine, as well as all the rest of these condensation products with piperazine, is very unstable at temperatures near its melting point, has an indefinite melting point depending considerably on the rate of heating, and is readily decomposed by acids.

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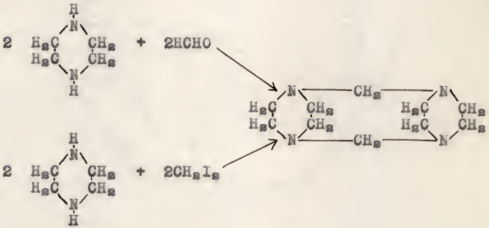
* For all reactions in this investigation involving an alkyl halide, the method used was that recommended by Cummings, Hopper and Wheeler[38].

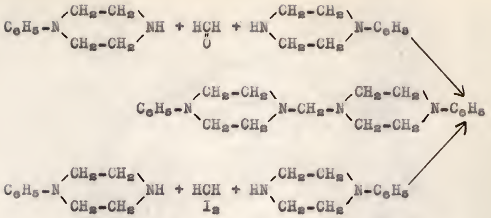
Formaldehyde and piperazine yielded the same product as was obtained from piperazine and methylene iodide.



Butyraldehyde and acetaldehyde gave with piperazine condensation products whose analyses apparently failed to support the above type of condensation. Analyses for nitrogen, carbon and hydrogen failed to give results from which a formula could be predicted.

All of these condensations were carried out with or without a solvent and in the absence of acid or alkali. The reactions usually proceeded rapidly with the evolution of heat. Since all of these compounds were insoluble, purification by recrystallization was impossible. Their instability rendered a vacuum distillation impossible. In order to obtain reasonably pure products the following procedure was used. The piperazine was dissolved in an appropriate solvent and filtered. This removed insoluble foreign matter. The aldehyde was freshly distilled, dissolved in an appropriate solvent and filtered. The aldehyde and piperazine were mixed and the resulting condensation product washed repeatedly with alcohol and ether.

From the above discussion it is evident that piperazine and aldehydes form a N,N′-bis-piperazyl alkyl methane type of compound or a polymer of this. In order to prevent the possibility of polymerization, N-monophenylpiperazine was condensed with aldehydes. When formaldehyde was condensed with N-monophenylpiperazine, the product obtained melted at 123 - 124° C.[84] When N-monophenylpiperazine was reacted with methylene iodide in the presence of alkali, the product had a melting point identical with that obtained from formaldehyde and the melting point of a mixture of the two melted at 123 - 124° C. This showed conclusively that the two products were identical. Their analysis indicated the expected structure, N-bis-(N′-phenyl piperazyl), methane.



N-monophenylpiperazine gave the same type product when condensed with benzaldehyde, acetaldehyde, p-tolylaldehyde, and anisaldehyde. Butyraldehyde gave a compound whose analysis did not check with the above type formula. Salicylaldehyde and o-chlorbenzaldehyde failed to give crystalline products. Due to their instability, purification by vacuum distillation could not be accomplished. All of the condensation products from N-monophenylpiperazine had a much lower melting point than the corresponding piperazine products and possessed solubilities which permitted purification by recrystallization.

When secondary amines are condensed with aldehydes in the presence of a reducing agent, the hydrogen attached to the nitrogen is replaced by the alkyl group corresponding to the aldehyde used. Although its use has been demonstrated, the reaction seems to have attained little general recognition as a means for the alkylation of amines. The application of this type of reaction to piperazine and N-monophenylpiperazine comprised another portion of this investigation.

Piperazine and N-monophenylpiperazine lend themselves quite readily to alkylation by this method. The alkyl derivatives obtained from these amines by the use of aldehydes were in most cases, much easier to purify and were usually obtained in better yields than the same products obtained by other methods. N,N'-dimethyl piperazine and N,N'-diethyl piperazine were prepared by the action of formaldehyde and acetaldehyde respectively on piperazine in the presence of powdered zinc and hydrochloric acid. Using this same reducing agent, N-phenyl, N'-methyl piperazine and N-phenyl, N'-ethyl piperazine were prepared by the respective action of formaldehyde and acetaldehyde on N-monophenylpiperazine. All of these compounds were obtained in very good yields and one distillation was sufficient to obtain a pure product. With only one exception, N-phenyl-N'-methylpiperazine, their boiling points checked favorably with those reported for the same compounds prepared by other methods. Zinc and hydrochloric acid worked very

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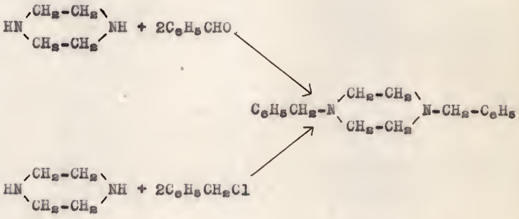
satisfactorily as the reducing agent for those aldehydes which were soluble in the hydrochloric acid, but failed to give results with the insoluble aldehydes even when enough alcohol was added to keep them in solution.

In order to carry out this reaction, the hydrochloride of the amine was dissolved in water. There was then added enough concentrated hydrochloric acid calculated to react with the zinc to be used. After addition of the aldehyde, powdered zinc was added gradually with stirring and cooling. Twice the calculated amount of zinc was used for the reduction, more hydrochloric acid being added if necessary. The mixture was then made alkaline and the free base extracted with ether. The ether solution was dried over anhydrous Na_2CO_3. The ether was then evaporated from the filtered solution and the free base purified by distillation.

Formic acid was used as the reducing agent for those aldehydes which were insoluble in hydrochloric acid. The formic acid method worked smoothly with aliphatic aldehydes, the time for the reaction being relatively short. However, with aromatic aldehydes the reaction velocity was very slow. In order to carry out these reactions, the amine and aldehyde were refluxed in a considerable excess of formic acid (90%) until the evolution of carbon dioxide had entirely ceased. The excess formic acid was evaporated on a water bath and the residue made alkaline. The base was extracted with ether, dried, recovered and purified by distillation or recrystallization.

N,N′-dibutyl piperazine was prepared by this method from piperazine and butyraldehyde. The alkylation proceeded smoothly and rapidly. N,N′-dibenzyl piperazine was prepared from piperazine and benzaldehyde. The reaction required five days of refluxing, but the yield was better than that obtained by the synthesis of the same compound from piperazine and benzyl chloride.



N,N′-di(p-methyl benzyl)piperazine was prepared by refluxing piperazine and p-tolylaldehyde in formic acid. Although the reaction proceeded very slowly and the yield was poor, the product was easily purified. Attempted alkylation by this method using anisaldehyde resulted in failure.

The use of other reducing agents is being contemplated for investigation in other problems so as to make alkylation by this method more applicable to aromatic aldehydes.

A very interesting type of compound was accidentally obtained in an attempt to prepare N,N′-di(β-trichlorethyl) piperazine from piperazine and chloral in the presence of zinc and hydrochloric acid. During the process of reaction it was deemed advantageous to heat the mixture since the reaction was proceeding very slowly. After the zinc had all reacted, the mixture was cooled and a very large amount of small white crystals separated. These were filtered off and recrystallized from 6N hydrochloric acid. The product separated in long rods. The purified product had no melting point, gave qualitative tests for carbon, nitrogen, zinc and chlorine and its water solution was strongly acidic. The analysis for chlorine and nitrogen indicated that the compound was $ZnCl_2\ C_4H_{10}N_2\cdot(HCl)_2$, zinc chloride piperazine dihydrochloride.

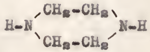
Before this phase of the work involving aldehydes had been conceived, plans had been made to prepare high molecular weight acid derivatives of piperazine and to study their physiological properties. In some preliminary work on this subject, two acid derivatives of piperazine were prepared. They were 1,4-piperazinium di-stearate and 1,4-piperazinium di-palmitate.

The formulae and properties of all compounds prepared during this investigation may be found in Table II.

TABLE I

Properties of Piperazine

Structural Formula



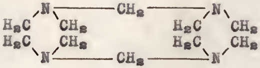
Synonyms	Diethylene diamine Hexahydro, 1,4-diazine Hexahydropyrazine
Formula of Hydrate	$C_4H_{10}N_2$ $6H_2O$
Molecular Weight(anhydrous)	86.09
(hydrate)	194.19
Melting Point(anhydrous)	105.6° C.
(hydrate)	44° C.
Boiling Point	146° C.
Solubilities (hydrate)	
Water	Very Soluble
Ethanol(95%)	Soluble
Ether	Slightly Soluble

TABLE II

Properties of Compounds

(1) N,N′-bis-piperazyl methane

Structural Formula



Method of Preparation

(a) Condensation of piperazine and formaldehyde

(b) Piperazine plus methylene iodide in alkaline solution

Melting Point	Not below 300° C.	
Molecular Weight	196.18	
Yield	(a) 97%	
	(b) 98%	
Analyses	Found	Calculated
Nitrogen,%	(a) 28.51	28.55
	(b) 28.67	28.55

Solubilities

Ethanol (95%)	Insoluble
Ether	Insoluble
Hexane	Insoluble
Water	Insoluble
Acetone	Insoluble

(2) Condensation of Piperazine and Acetaldehyde

Structural Formula

No formula assigned

Method of Preparation

Condensation of piperazine and acetaldehyde

Melting Point	Not below 300° C.
Molecular Weight	?
Yield	11 g.
Analyses	Found
Nitrogen,%	11.80
Carbon,%	66.80
Hydrogen,%	9.80

Solubilities

Ethanol (95%)	Insoluble
Ether	Insoluble
Hexane	Insoluble
Water	Insoluble
Acetone	Insoluble
Benzene	Insoluble

(3) Condensation of Piperazine and Butyraldehyde

Structural Formula

No formula assigned

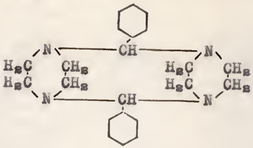
Method of Preparation

Condensation of piperazine and butyraldehyde

Melting Point	258 - 260° C. with decomp.
Molecular Weight	?
Yield	14 g.
Analyses	Found
Nitrogen, %	16.30
Carbon, %	74.50
Hydrogen, %	8.50
Solubilities	
Ethanol (95%)	Insoluble
Ether	Insoluble
Hexane	Insoluble
Water	Insoluble
Acetone	Insoluble
Benzene	Insoluble

(4) N,N′-bis-piperazyl, phenyl methane

Structural Formula



Method of Preparation

(a) Condensation of piperazine and benzaldehyde

(b) Piperazine plus benzal chloride in alkaline solution

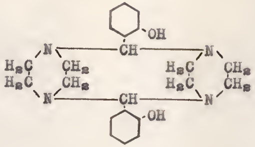
Melting Point	(a) 270° C. with decomposition	
	(b) 265° C. with decomposition	
Molecular Weight	348.25	
Yield	(a) 98%	
	(b) 46%	
Analyses	Found	Calculated
Nitrogen, %	(a) 16.12	16.09
	(b) 15.93	16.09

Solubilities

Ethanol (95%)	Insoluble
Ether	Insoluble
Hexane	Insoluble
Water	Insoluble
Acetone	Insoluble
Benzene	Insoluble

(5) N,N′-bis-piperazyl, o-hydroxyphenyl methane

Structural Formula



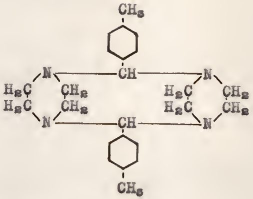
Method of Preparation

Condensation of piperazine and salicylaldehyde

Melting Point	210 - 211° C. with decomp.	
Molecular Weight	380.25	
Yield	44%	
Analysis	Found	Calculated
Nitrogen, %	14.70	14.73
Solubilities		
Ethanol (95%)	Insoluble	
Ether	Insoluble	
Hexane	Insoluble	
Water	Insoluble	
Acetone	Insoluble	
Benzene	Insoluble	

(6) N,N′-bis-piperazyl, p-methylphenyl methane

Structural Formula



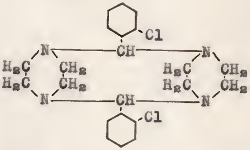
Method of Preparation

Condensation of piperazine and p-tolylaldehyde

Melting Point	275° C. with decomposition	
Molecular Weight	376.28	
Yield	90%	
Analysis	Found	Calculated
Nitrogen, %	15.12	14.88
Solubilities		
Ethanol (95%)	Insoluble	
Ether	Insoluble	
Hexane	Insoluble	
Water	Insoluble	
Acetone	Insoluble	
Benzene	Insoluble	

(7) N,N'-bis-piperazyl, o-chlorophenyl methane

Structural Formula



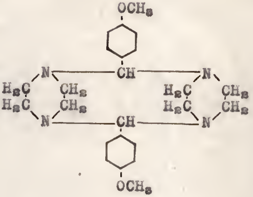
Method of Preparation

Condensation of piperazine and o-chlorobenzaldehyde

Melting Point	240° C. with decomposition	
Molecular Weight	417.15	
Yield	95%	
Analysis	Found	Calculated
Nitrogen, %	13.37	13.43
Solubilities		
Ethanol (95%)	Insoluble	
Ether	Insoluble	
Hexane	Insoluble	
Water	Insoluble	
Acetone	Insoluble	
Benzene	Insoluble	

(8) N,N'-bis-piperazyl, p-methoxyphenyl methane

Structural Formula



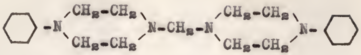
Method of Preparation

Condensation of piperazine and anisaldehyde

Melting Point	290° C. with decomposition	
Molecular Weight	408.28	
Yield	85%	
Analysis	Found	Calculated
Nitrogen, %	13.72	13.72
Solubilities		
Ethanol (95%)	Insoluble	
Ether	Insoluble	
Hexane	Insoluble	
Water	Insoluble	
Acetone	Insoluble	
Benzene	Insoluble	

(9) N-bis-(N'-phenylpiperazyl), methane

Structural Formula



Method of Preparation

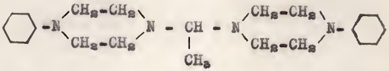
(a) Condensation of N-monophenylpiperazine and formaldehyde

(b) N-monophenylpiperazine plus methylene iodide in alkaline solution

Melting Point	(a) 123 - 124° C.	
	(b) 123 - 124° C.	
Molecular Weight	336.25	
Yield	(a) 79%	
	(b) 24%	
Analyses	Found	Calculated
Nitrogen, %	(a) 16.58	16.66
	(b) 16.74	16.66
Solubilities		
Ethanol (95%)	Slightly Soluble Cold	
	Soluble Hot	
Ether	Soluble	
Hexane	Slightly Soluble	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(10) N-bis-(N′-phenylpiperazyl), ethane

Structural Formula



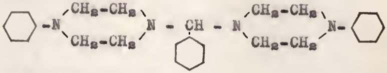
Method of Preparation

Condensation of N-monophenylpiperazine and acetaldehyde

Melting Point	121 - 123° C.	
Molecular Weight	350.26	
Yield	25%	
Analysis	Found	Calculated
Nitrogen, %	15.82	16.00
Solubilities		
Ethanol (95%)	Soluble	
Ether	Soluble	
Hexane	Slightly Soluble Cold Soluble Hot	
Water	Insoluble	
Acetone	Slightly Soluble	
Benzene	Soluble	

(14) N-bis-(N′-phenylpiperazyl), phenyl methane

Structural Formula



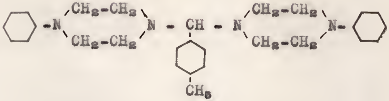
Method of Preparation

Condensation of N-monophenylpiperazine and benzaldehyde

Melting Point	125 - 126° C.	
Molecular Weight	412.28	
Yield	90%	
Analysis	Found	Calculated
Nitrogen, %	13.54	13.59
Solubilities		
Ethanol (95%)	Soluble	
Ether	Insoluble	
Hexane	Slightly Soluble Cold Soluble Hot	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(15) N-bis-(N'-phenylpiperazyl), p-methylphenyl methane

Structural Formula



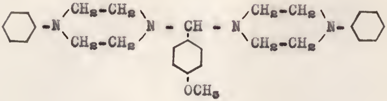
Method of Preparation

Condensation of N-monophenylpiperazine and p-tolylaldehyde

Melting Point	144 - 145° C.	
Molecular Weight	426.29	
Yield	83%	
Analysis	Found	Calculated
Nitrogen, %	13.29	13.14
Solubilities		
Ethanol (95%)	Insoluble	
Ether	Insoluble	
Hexane	Slightly Soluble Cold Soluble Hot	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(16) N-bis-(N′-phenylpiperazyl), p-methoxyphenyl methane

Structural Formula



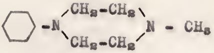
Method of Preparation

Condensation of N-monophenylpiperazine and anisaldehyde

Melting Point	135 - 136° C.	
Molecular Weight	442.29	
Yield	67%	
Analysis	Found	Calculated
Nitrogen, %	12.67	12.67
Solubilities		
Ethanol (95%)	Soluble	
Ether	Insoluble	
Hexane	Insoluble Cold Soluble Hot	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(17) N-phenyl-N′-methyl piperazine

Structural Formula



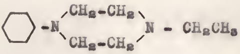
Method of Preparation

N-monophenylpiperazine plus formaldehyde in the presence of zinc and HCl

Boiling Point	109 - 110° C. at 5 mm.	
	Oil Bath Temp. 168 - 170° C.	
Molecular Weight	176.14	
Yield	42%	
Analysis	Found	Calculated
Nitrogen, %	15.95	15.91
Solubilities		
Ethanol (95%)	Soluble	
Ether	Soluble	
Hexane	Slightly Soluble	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(18) N-phenyl-N′-ethyl piperazine

Structural Formula



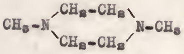
Method of Preparation

N-monophenylpiperazine plus acetaldehyde in the presence of zinc and HCl

Boiling Point	144.5 - 145.5° C. at 10 mm.	
	Oil Bath Temp. 186 - 189° C.	
Molecular Weight	190.16	
Yield	98%	
Analysis	Found	Calculated
Nitrogen, %	14.81	14.74
Solubilities		
Ethanol (95%)	Soluble	
Ether	Soluble	
Hexane	Slightly Soluble	
Acetone	Soluble	
Benzene	Soluble	
Water	Insoluble	

(19) N,N'-dimethyl piperazine

Structural Formula



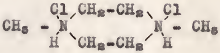
Method of Preparation

Piperazine plus formaldehyde in the presence of zinc and HCl

Boiling Point	130 - 135° C.	
Molecular Weight	114.12	
Yield	88%	
Analysis	Found	Calculated
Nitrogen, %	24.51	24.56
Solubilities		
Ethanol (95%)	Soluble	
Ether	Soluble	
Hexane	Slightly Soluble	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(20) N,N′-dimethyl piperazine dihydrochloride

Structural Formula



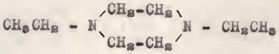
Method of Preparation

N,N′-dimethyl piperazine plus HCl

Melting Point	263° C. with decomposition	
Molecular Weight	187.05	
Yield	74%	
Analysis	Found	Calculated
Nitrogen, %	14.83	14.97
Solubilities		
Ethanol (95%)	Slightly Soluble Cold Soluble Hot	
Ether	Insoluble	
Hexane	Insoluble	
Water	Soluble	
Acetone	Insoluble	
Benzene	Insoluble	

(21) N,N′-diethyl piperazine

Structural Formula



Method of Preparation

Piperazine plus acetaldehyde in the presence of zinc and HCl

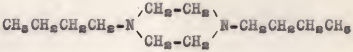
Boiling Point	174 - 177° C.	
Molecular Weight	142.15	
Yield	92%	
Analysis	Found	Calculated
Nitrogen, %	19.69	19.71

Solubilities

Ethanol (95%)	Soluble
Ether	Soluble
Hexane	Slightly Soluble
Water	Insoluble
Acetone	Soluble
Benzene	Soluble

(22) N,N′-dibutyl piperazine

Structural Formula



Method of Preparation

Piperazine plus butyraldehyde in the presence of formic acid

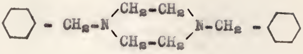
Boiling Point	195 - 195.5° C. at 12 mm.	
	Oil Bath Temp. 247 - 249° C.	
Molecular Weight	198.22	
Yield	92%	
Analysis	Found	Calculated
Nitrogen, %	14.15	14.14

Solubilities

Ethanol (95%)	Soluble
Ether	Soluble
Hexane	Slightly Soluble
Water	Insoluble
Acetone	Soluble
Benzene	Soluble

(23) N,N′-dibenzyl piperazine

Structural Formula



Method of Preparation

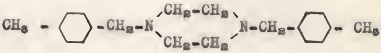
(a) Piperazine plus benzaldehyde in the presence of formic acid

(b) Piperazine plus benzyl chloride in alkaline solution

Melting Point	(a) 91.5 - 92° C.	
	(b) 92 - 93° C.	
Molecular Weight	266.19	
Yield	(a) 84%	
	(b) 75%	
Analyses	Found	Calculated
Nitrogen, %	(a) 10.60	10.53
	(b) 10.83	10.53
Solubilities		
Ethanol (95%)	Soluble	
Ether	Soluble	
Hexane	Soluble	
Water	Insoluble	
Acetone	Soluble	
Benzene	Soluble	

(24) N,N'-di(p-methyl benzyl) piperazine

Structural Formula



Method of Preparation

Piperazine plus p-tolylaldehyde in the presence of formic acid

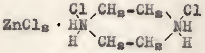
Melting Point	101 - 102° C.	
Molecular Weight	294.22	
Yield	31%	
Analysis	Found	Calculated
Nitrogen, %	9.54	9.53

Solubilities

Ethanol (95%)	Soluble
Ether	Soluble
Hexane	Soluble
Water	Insoluble
Acetone	Soluble
Benzene	Soluble

(25) Zinc chloride, piperazine dihydrochloride

Structural Formula



Method of Preparation

Piperazine plus $ZnCl_2$ in HCl solution

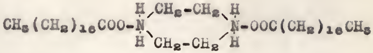
Melting Point	Not under 300° C.	
Molecular Weight	295.31	
Yield	95%	
Analyses	Found	Calculated
Nitrogen, %	9.38	9.48
Chlorine, %	48.22	48.07

Solubilities

Ethanol (95%)	Insoluble
Ether	Insoluble
Hexane	Insoluble
Water	Soluble
Acetone	Insoluble
Benzene	Insoluble

(26) 1,4-Piperazinium di-stearate

Structural Formula



Method of Preparation

Piperazine plus stearic acid

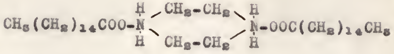
Melting Point	101 - 101.5° C.	
Molecular Weight	654.66	
Yield	82%	
Analyses	Found	Calculated
Nitrogen, %	4.41	4.28
Carbon, %	72.86	73.33
Hydrogen, %	12.96	12.63

Solubilities

Ethanol (95%)	Slightly Soluble Cold Soluble Hot
Ether	Insoluble
Hexane	Insoluble
Water	Insoluble
Acetone	Insoluble
Benzene	Insoluble

(27) 1,4-Piperazinium di-palmitate

Structural Formula



Method of Preparation

Piperazine plus palmitic acid

Melting Point	98 - 99° C.	
Molecular Weight	598.60	
Yield	96%	
Analyses	Found	Calculated
Nitrogen, %	4.80	4.69
Carbon, %	72.25	72.24
Hydrogen, %	12.35	12.37

Solubilities

Ethanol (95%)	Slightly Soluble Cold Soluble Hot
Ether	Insoluble
Hexane	Insoluble
Water	Insoluble
Acetone	Insoluble
Benzene	Insoluble

EXPERIMENTAL PART*

(1)** N,N'-bis-piperazyl methane

$$\begin{array}{l} \text{CH}_2\text{-NC}_4\text{H}_8\text{N} \\ \text{NC}_4\text{H}_8\text{N-H}_2\text{C} \end{array}$$

To 8 g. of anhydrous piperazine suspended in a small amount of anhydrous ether was added excess paraformaldehyde. The mixture was placed under a reflux condenser and heated until the ether began to boil. After the source of heat was removed, bubbles of gas continued to pass off slowly for about twenty minutes. Evaporation of the ether left a white solid. After drying, the product was boiled with mineral spirits (B. P. 170° C.) in order to liberate the excess paraformaldehyde which sublimes at 120° C. The mixture was filtered and the cream colored solid washed thoroughly with petroleum ether. Although darkening slightly, the product did not melt under 300° C. Before analysis, the compound was dried for two hours at 150° C. Its composition was indicated by a Kjeldahl analysis.

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*The properties, yields and analyses of all compounds whose preparation is listed in this section, are given in Table II.

**The numbers of compounds, as listed in this experimental part, correspond to the numbers under which they are listed in Table II.

The same compound was prepared from piperazine and methylene iodide. Twelve grams (excess) piperazine hexahydrate was dissolved in 100 cc. of water and filtered in order to remove any suspended impurities. This was added to a filtered solution of 20 g. of sodium carbonate in 100 cc. water. After the addition of 14.21 g. of methylene iodide, the mixture was refluxed for three hours. The light tan colored product was filtered and washed with water until the filtrate no longer tested basic. It was then dried between plates, powdered and washed thoroughly with alcohol and ether. The physical properties of this compound agreed exactly with those of the product obtained from formaldehyde and its composition was indicated by a Kjeldahl analysis. Analyses, properties etc. for these products are listed in Table II.

(2) Condensation of Piperazine and Acetaldehyde

Ten grams of piperazine hexahydrate was dissolved in water, filtered, cooled in an ice bath and excess acetaldehyde added. There was no apparent reaction after one hour. The solution was removed from the ice bath and, after standing for two hours at room temperature, it had turned yellow. After twelve more hours a thick mass of bright yellow precipitate had formed. The reaction mixture was filtered and the product washed with water. It did not melt below 300° C. and exhibited no indications of water of crystallization. It was dried for two hours at 120° C. and placed under vacuum over anhydrous KOH. Analysis for nitrogen by the Kjeldahl method and analysis for carbon and hydrogen by the furnace method indicated that carbon, hydrogen and nitrogen were not the only constituent elements. No formula could be predicted from the analytical data. All data for this compound are given in Table II.

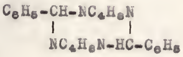
The same compound was obtained when molar quantities of piperazine hexahydrate and acetaldehyde were used. However, the yield was very poor.

(3) Condensation of Piperazine and Butyraldehyde

A filtered alcoholic solution of 19.4 g. piperazine hexahydrate was added to a filtered alcoholic solution of 7.2 g. butyraldehyde. The reaction proceeded immediately with the formation of a white precipitate. This was filtered and washed thoroughly with alcohol and ether. Fourteen grams of a fine white, amorphous powder was obtained. It began darkening at about 250° C.

and melted at 258 - 260° C. Before analysis, it was dried at 120° C. for two hours and over anhydrous KOH under vacuum. Kjeldahl analysis for nitrogen and combustion furnace analysis for carbon and hydrogen indicated that the compound contained only these three constituent elements. However, a satisfactory formula was not derived. Further data for this compound are listed in Table II.

(4) N,N′-bis-piperazyl, phenyl methane

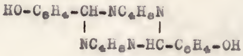


$$\begin{array}{l} C_6H_5\text{-}CH\text{-}NC_4H_8N \\ \qquad\quad | \qquad\qquad | \\ \qquad\; NC_4H_8N\text{-}HC\text{-}C_6H_5 \end{array}$$

Twenty grams of piperazine hexahydrate was dissolved in as small amount of cold alcohol as possible. This was filtered and 10.6 g. freshly distilled benzaldehyde was added. A white precipitate began forming within about two minutes and soon became very thick. The product was filtered and thoroughly washed with alcohol and ether. It melted with decomposition at about 270° C. Before analysis, the product was dried for two hours at 120° C. A Kjeldahl analysis indicated its composition. Analysis, properties etc. are listed in Table II.

The same compound was prepared from piperazine and benzalchloride. Eight grams of benzalchloride was added to a filtered aqueous solution of 12 g. sodium carbonate and slight excess piperazine hexahydrate. The mixture was refluxed for two hours. After standing overnight, an abundant quantity of a white precipitate had formed mixed with some unreacted benzalchloride. This was filtered and washed thoroughly with hot alcohol and ether and finally dried for one hour at 120° C. and under vacuum over solid KOH. Its melting point was about 265° C. with decomposition and this value was unchanged when mixed with the compound obtained from benzaldehyde. Kjeldahl analysis indicated its composition. All the data for these products are recorded in Table II.

(5) N,N′-bis-piperazyl, o-hydroxy phenyl methane

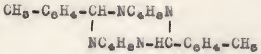


$$\begin{array}{lll} HO-C_6H_4-CH- & NC_4H_8N & \\ \qquad\qquad\quad | & \qquad\quad | & \\ \qquad\qquad\quad NC_4H_8N & -HC-C_6H_4-OH & \end{array}$$

Five grams of piperazine hexahydrate was treated with 3 g. of freshly distilled salicylaldehyde. After standing overnight, a yellow solid had formed. This was suspended in alcohol, filtered and washed thoroughly with alcohol and ether. The product was dried at 120° C. for one hour and then under vacuum over solid KOH. A Kjeldahl analysis for nitrogen indicated its composition.

At 210 - 211° C. it melted with boiling and with the formation of a red liquid. Further data are listed in Table II.

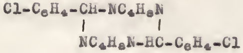
(6) N,N'-bis-piperazyl, p-methyl phenyl methane



$$\begin{array}{l} CH_3-C_6H_4-CH-NC_4H_8N \\ \qquad\qquad\qquad\;\; | \qquad\qquad\;\; | \\ \qquad\qquad\qquad\;\; NC_4H_8N-HC-C_6H_4-CH_3 \end{array}$$

Ten grams of piperazine hexahydrate was treated with 6 g. p-tolylaldehyde. The mixture solidified into a white solid mass after standing a few hours. Alcohol was added and the solid mass crushed. The material was filtered and washed thoroughly with alcohol and ether. The product was then dried at 120° C. for one hour and placed in a desiccator with solid KOH. Its composition was indicated by a Kjeldahl analysis. Analysis, properties etc. are recorded in Table II.

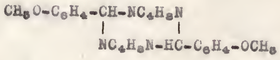
(7) N,N'-bis-piperazyl, o-chlorophenyl methane



$$\begin{array}{l} Cl-C_6H_4-CH-NC_4H_8N \\ \qquad\qquad\quad\; | \qquad\qquad\;\; | \\ \qquad\qquad\quad\; NC_4H_8N-HC-C_6H_4-Cl \end{array}$$

Nine and seven tenths grams of piperazine hexahydrate was mixed with 7 g. o-chlorobenzaldehyde. Reaction started immediately and within five minutes the mixture had solidified into a hard mass. After standing overnight, the product was crushed and treated with hot alcohol. After filtering and washing thoroughly with alcohol and ether, the white product was dried between porous plates. Before analysis it was dried at 120° C. for one hour and placed in a vacuum over KOH. Drying in the oven caused the product to turn slightly yellow. A Kjeldahl analysis for nitrogen determined its composition. Data for this compound are listed in Table II.

(8) N,N′-bis-piperazyl, p-methoxyphenyl methane



$$\begin{array}{l} CH_3O\text{-}C_6H_4\text{-}CH\text{-}NC_4H_8N \\ \qquad\qquad\qquad | \qquad\quad\; | \\ \qquad\qquad\qquad NC_4H_8N\text{-}HC\text{-}C_6H_4\text{-}OCH_3 \end{array}$$

A mixture of 13.6 g. anisaldehyde and 19.4 g. piperazine hexahydrate was heated on a steam bath for ten minutes. A curdy white mass began to form and, on standing overnight, the entire mass solidified. This solid was pulverized and treated repeatedly with hot alcohol and finally washed thoroughly with alcohol and ether. The product was dried over P_2O_5 under vacuum and its composition determined by a Kjeldahl analysis. Yields, properties etc. are recorded in Table II.

(9) N-bis-(N$'$-phenyl piperazyl), methane

$$C_6H_5-NC_4H_8N-CH_2-NC_4H_8N-C_6H_5$$

To 16 g. N-monophenylpiperazine was added 1.5 g. paraformaldehyde. There was no apparent reaction in the cold. The mixture was placed on a steam bath. Within a few seconds it started bubbling and immediately foamed giving the appearance of a very violent reaction which ceased after a few seconds of activity. After the reaction had ceased, the mixture was removed from the steam bath. On cooling, it solidified into a white crystalline mass. Water was added to the insoluble product and the mixture was boiled and filtered. This was to remove any unreacted paraformaldehyde. The crude product was dissolved in boiling alcohol and filtered. On cooling, white crystals separated in the form of needle clusters. After two more recrystallizations from hot alcohol a pure product was obtained. Its melting point was not raised by an additional recrystallization from a freezing mixture of benzene and petroleum ether. Its composition was determined by a Kjeldahl analysis for nitrogen.

The same compound was obtained from N-monophenylpiperazine and methylene iodide. Sixteen grams of N-monophenylpiperazine was suspended in 200 cc. of water containing 10.6 g. Na_2CO_3. Thirteen grams of methylene iodide was added and the mixture placed under a reflux. When heat was applied the reaction started immediately and, within a few seconds, became very violent. Much heat was liberated and considerable decomposition with blackening took place. The mixture was refluxed for three hours. On cooling, a mixture of black oil and white crystals separated. The reaction mixture was extracted with ether and the ether solution dried over anhydrous Na_2CO_3. A red oil was left after evaporating the ether, however the oil solidified when cooled in an ice bath. This was dissolved in boiling heptane but a red oil again appeared on cooling. The oil was separated from the heptane and dissolved in alcohol. A cream colored precipitate separated on cooling. After two more recrystallizations from alcohol, using Norite as a decolorizing agent, white crystals were obtained. This product showed its identity with that from N-monophenylpiperazine and formaldehyde by a mixed melting point and by a subsequent Kjeldahl analysis for nitrogen. Yields, properties etc. of these products are listed in Table II.

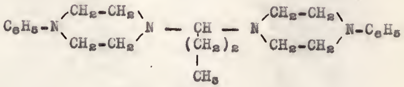
(10) N-bis-(N$'$-phenylpiperazyl), ethane

$$C_6H_5-NC_4H_8N-CH(CH_3)-NC_4H_8N-C_6H_5$$

Thirty-two and four tenths grams of N-monophenylpiperazine and excess acetaldehyde were dissolved in separate portions of ether. After cooling each in an ice salt bath, the solutions were poured together slowly with stirring. A white precipitate separated. This was filtered off and the ether solution evaporated. There remained an amber colored oil whose composition was not determined. The white precipitate was found to be soluble in most organic solvents but decomposed quite readily when boiled in most of these solvents. It decomposed into an oil when boiled with water. On recrystallization from boiling heptane the product separated as a light yellow solid. Since the compound was apparently unstable, no further recrystallizations were attempted. The recrystallized product was dried over P_2O_5 under vacuum and its composition determined by a Kjeldahl analysis. Further data for this compound are listed in Table II.

(11) Condensation of N-monophenylpiperazine and Butyraldehyde

When the ether solutions of 8.1 g. N-monophenylpiperazine and 1.8 g. butyraldehyde were mixed, a white precipitate formed immediately. This was filtered and washed with ether. Since the product was apparently slightly soluble in ether, some of the compound was lost by washing. After recrystallizations from boiling heptane, the compound melted at 122 - 123° C. The yield was 5 g. of white, fine needle shaped crystals. The product was soluble in alcohol and dissolved in warm water with apparent decomposition. A Kjeldahl analysis showed the compound to contain 12.42% nitrogen. 15.07% is the theoretical percent nitrogen for the expected compound,



A second attempt was made to prepare this compound and this attempt met with the same results. No formula was predicted for the product obtained.

(12) Condensation of N-monophenylpiperazine and Salicylaldehyde

Three and one tenth grams of salicylaldehyde was added to an ether solution of 8.1 g. N-monophenylpiperazine. There was no evidence of reaction after standing overnight. The ether was evaporated and the mixture heated on a steam bath for one-half hour. A thick yellow oil remained which became more viscous on moderate cooling and solidified into a hard, brittle, amber colored resin when cooled in an ice bath. However, the resin softened when left at room temperature. The product was soluble in alcohol and ether and insoluble in water. Attempts were made to recrystallize the product from an alcohol, water mixture and from heptane. In each case, a yellow solid separated when the solution was cooled in an ice, salt bath but the solid became an oil when the mixture was filtered.

(13) Condensation of N-monophenylpiperazine and o-chlorobenzaldehyde

When 3.5 g. o-chlorobenzaldehyde was added to 0.05 moles of N-monophenylpiperazine a semi-solid mass was obtained which did not lend itself to purification by recrystallization.

(14) N-bis-(N′-phenylpiperazyl), phenyl methane

$$C_6H_5\text{-}NC_4H_8N\text{-}CH(C_6H_5)\text{-}NC_4H_8N\text{-}C_6H_5$$

When 10.6 g. freshly distilled benzaldehyde was added to 32.4 g. N-monophenylpiperazine, reaction started immediately with the liberation of heat. The mixture became a thick white paste and a white solid remained after the reaction mixture had been washed with ether. The product was dissolved in heptane. White, needle shaped crystals separated in clusters when the heptane solution was cooled slowly. Three recrystallizations were sufficient to obtain a pure product. After drying over solid KOH under vacuum, the composition of the compound was determined by a Kjeldahl analysis for nitrogen. Data for this compound are listed in Table II.

(15) N-bis-(N'-phenylpiperazyl), p-methylphenyl methane

$C_6H_5-NC_4H_8N-CH(C_6H_4-CH_3)-NC_4H_8N-C_6H_5$

Three grams of freshly distilled p-tolylaldehyde was added to an ether solution of 8.1 g. N-monophenylpiperazine. White crystals were formed when the mixture stood overnight. This was filtered, washed and recrystallized twice from boiling heptane. The product separated from the recrystallization solvent in white needle shaped crystals. The compound was dried at 120° C. for one hour and placed over solid KOH under vacuum. Its composition was determined by a Kjeldahl analysis for nitrogen. Yields, properties etc. are recorded in Table II.

(16) N-bis-(N′-phenylpiperazyl), p-methoxyphenyl methane

$C_6H_5-NC_4H_8N-CH(C_6H_4-OCH_3)-NC_4H_8N-C_6H_5$

To 16.2 g. N-monophenylpiperazine was added 6.8 g. anisaldehyde. Reaction started immediately with the liberation of heat and the formation of a white solid. This solid was dissolved in ether and filtered. When the beaker containing the ethereal solution was scratched, crystals began to precipitate out. After five minutes a large quantity had separated. The crystalline product was filtered and recrystallized three times from hexane. After drying for several days over P_2O_5 under vacuum, the composition of the compound was determined by an analysis for nitrogen by the Kjeldahl method. Data for this compound are listed in Table II.

(17) N-phenyl-N′-methyl piperazine

$C_6H_5-NC_4H_8N-CH_3$

Twenty-one and five tenths grams of purified N-monophenylpiperazine dihydrochloride was dissolved in 100 cc. water. Ten cubic centimeters of concentrated hydrochloric acid were added and the mixture stirred and cooled in an ice bath. This was treated with 15 cc. formaldehyde solution (40%) and 18 g. zinc dust added. Fifty cubic centimeters of concentrated hydrochloric acid were added gradually with constant stirring, care being taken to keep the temperature low. After one hour the mixture was removed from the ice bath and stirred three more hours. On being made alkaline with 50% KOH, a yellow oil separated. This was extrated with ether and the ether solution dried over anhydrous Na_2CO_3. The dried solution was filtered, the ether evaporated and the amine purified by distillation under reduced pressure. The boiling point of the compound was 109 - 110° C. at 5 mm. (Prelog and Stephan[45] reported 140 - 142° C. at 3 mm.) The yield was poor due to another reaction product which appeared as a solid residue in the distilling flask. The composition of this residue was not determined. The composition of the N-phenyl-N'-methyl piperazine was determined by a Kjeldahl analysis for nitrogen. Properties, yield etc. are listed in Table II.

(18) N-phenyl-N'-ethyl piperazine

$C_6H_5-NC_4H_8N-C_2H_5$

Twenty- three and five tenths grams (0.1 mole) of N-monophenylpiperazine dihydrochloride was dissolved in 100 cc. water containing 10 cc. concentrated hydrochloric acid. The mixture was cooled in an ice bath and 10 g. (excess) acetaldehyde and 17 g. zinc dust were added with stirring. With cooling and constant stirring, 40 cc. concentrated hydrochloric acid was added gradually so that the temperature did not rise above 20° C. After one hour the mixture was removed from the ice and stirred at room temperature for four hours. It was made alkaline with 50% KOH and a clear oil, which had a characteristic amine odor, separated. The amine was extracted with ether and the ethereal solution dried over anhydrous Na_2CO_3. The filtered solution was evaporated and the amine rectified by distillation under reduced pressure. Nearly all of the product came over within a temperature range of 144.5 - 145.5° C. at 10 mm. (Prelog and Stephan[45] reported 157 - 158° C. at 10 mm.) Its composition was determined by a Kjeldahl analysis for nitrogen. All data for this compound are listed in Table II.

(19) N,N′-dimethyl piperazine

$CH_3-NC_4H_8N-CH_3$

Nineteen and four tenths grams of piperazine hexahydrate was added to 100 cc. water containing 28 cc.

of concentrated hydrochloric acid. The solution was cooled in an ice bath and treated with 16.8 g. of a 40% formaldehyde solution and 35 g. zinc dust. One hundred twelve cubic centimeters of concentrated hydrochloric acid was added gradually with cooling and continuous stirring. The reaction mixture was then stirred for three hours at room temperature and then heated on a steam bath until warm. After cooling, the unused zinc was filtered off and the solution made basic with 50% NaOH solution. The colorless oil which separated had a sharp amine odor and fumed in the presence of hydrogen chloride. The product was extracted with ether, dried over anhydrous Na_2SO_4, filtered and evaporated. The amine was distilled and analyzed for nitrogen by the Kjeldahl method. The boiling point of this compound was 130 - 135° C. Boiling points ranging from 131° C. to 158° C. have been reported by other investigators[39, 40, 41] who prepared this amine by other methods. Additional data for this compound are listed in Table II.

(20) N,N′-dimethyl piperazine dihydrochloride

$$CH_3-NC_4H_8N-CH_3\cdot 2HCl$$

Three grams of N,N′-dimethyl piperazine was dissolved in alcohol and the calculated quantity of concentrated hydrochloric acid was added. When ether was added to the cooled solution, white crystals separated. These were filtered, washed with ether and recrystallized from alcohol. The composition of the salt was indicated by a Kjeldahl analysis for nitrogen. Yield, properties etc. are listed in Table II.

(21) N,N′-diethyl piperazine

$C_2H_5-NC_4H_8N-C_2H_5$

Nineteen and four tenths grams of piperazine hexahydrate was added to 100 cc. water containing 28 cc. concentrated hydrochloric acid, and the mixture cooled in an ice bath. Thirteen grams of acetaldehyde and 35 g. zinc dust were added. One hundred twelve cubic centimeters of concentrated hydrochloric acid were added gradually and the reaction mixture was stirred for one hour. It was then removed from the ice bath and stirred four more hours. By that time, practically all the zinc had reacted. After standing all night, the mixture was made strongly alkaline with 50% KOH. The oil which had separated was extracted with ether and the ethereal solution dried over solid KOH. The filtered solution was evaporated and the amine was purified by distillation. A small amount of the dihydrochloride was prepared by passing dry HCl into an anhydrous ether solution of the free base. The salt was very hygroscopic. After recrystallization from butanol, it melted at 281° C. with decomposition. The composition of the free base was determined by a Kjeldahl analysis for nitrogen. Yields, properties etc. are listed in Table II. The boiling point of the free base was 174 - 177° C. Other investigators[40,42] reported boiling points of 165° C. and 185° C. for the same compound prepared by other methods. Schmidt and Wichmann[40] reported 277° C. as the melting point of the dihydrochloride.

(22) N,N′-dibutyl piperazine

$C_4H_9-NC_4H_8N-C_4H_9$

A mixture of 20 g. piperazine hexahydrate, 14.4 g. butyraldehyde and 80 cc. of 90% formic acid was placed under a reflux condenser and heated. A rapid evolution of carbon dioxide began as soon as the mixture began to boil. The refluxing was continued for forty-eight hours. The mixture was transferred to an evaporating dish and heated on a water bath until the formic acid was completely evaporated. On cooling, a few crystals appeared, mixed with a thick red oil. The mixture was made alkaline with 50% KOH. An amber-colored oil separated.

This was extracted with ether and the ethereal solution was dried over anhydrous Na_2CO_3. The ether was evaporated from the filtered solution and the amine was distilled under reduced pressure. Its composition was determined by a Kjeldahl analysis for nitrogen. Data for this compound are listed in Table11.

(23) N,N′-dibenzyl piperazine

$C_6H_5CH_2-NC_4H_8N-CH_2C_6H_5$

A mixture of 12 g. piperazine hexahydrate, 40 cc. formic acid (90%) and 10.6 g. benzaldehyde was refluxed five days. A slow evolution of carbon dioxide began as soon as the refluxing started. The mixture was evaporated on a water bath until no odor of formic acid could be detected. The remaining thick red oil was made alkaline with 50% KOH. A brown semi-solid mass separated. The alkaline solution was poured off and the product washed with water. When the residue was treated with ice and water, the paste solidified into a yellow solid. This was extracted with ether. After evaporation of the ether, the residual oil solidified into a cream colored solid on cooling. The solid was recrystallized from 60% alcohol. After two recrystallizations the product separated in slender needle shaped crystals. A Kjeldahl analysis for nitrogen indicated its composition.

The same compound was prepared from piperazine and benzyl chloride. Nineteen and four tenths grams of piperazine hexahydrate was dissolved in 100 cc. water. To this was added 200 cc. water containing 22 g. sodium carbonate. Twenty-five and two tenths grams of benzyl chloride was added and the mixture refluxed one hour. On cooling, the oily layer solidified. This was filtered and washed with water until the filtrate no longer tested alkaline. The crude product was recrystallized twice from 60% alcohol, dried over solid KOH under vacuum and analyzed for nitrogen by the Kjeldahl method. A mixed melting point showed it to be identical with the compound obtained from piperazine and benzaldehyde. Data for these products are listed in Table II.

(24) N,N′-di(p-methyl benzyl) piperazine

$$CH_3-C_6H_4-CH_2-NC_4H_8N-CH_2-C_6H_4-CH_3$$

A mixture of 11 g. piperazine hexahydrate, 40 cc. formic acid (90%) and 12 g. p-tolylaldehyde was refluxed for five days. Carbon dioxide was evolved very slowly. The excess formic acid was evaporated on a water bath and the residual oil made alkaline with 50% KOH. The mixture was extracted with ether. On evaporation of the ether extract, a red oil was left. This solidified into a cream colored paste on cooling. When placed on a porous plate, the oily part of the mixture was absorbed and a white solid was left on the plate. This was recrystallized twice from 60% alcohol. The product separated from the solvent in the form of slender white needles. Its composition was determined by a Kjeldahl analysis for nitrogen. Yield, properties etc. are recorded in Table II.

(25) Zinc chloride, piperazine dihydrochloride

$$ZnCl_2 \cdot C_4H_{10}N_2 \cdot (HCl)_2$$

This compound was accidentally obtained in an attempt to prepare N,N -di-β-trichloroethyl piperazine from piperazine and chloral in the presence of zinc and hydrochloric acid. This accounts for the proceedure given below.

Nineteen and four tenths grams of piperazine hexahydrate was dissolved in 100 cc. water containing 28 cc. concentrated hydrochloric acid. Twenty-nine and five tenths grams of chloral and 35 g. zinc dust were added. The mixture was then treated with 100 cc. concentrated hydrochloric acid. The temperature immediately rose to about 65° C. The mixture was stirred for three hours. A white precipitate settled out of the cooled solution. The mixture was warmed until solution of the precipitate had taken place and then filtered in order to remove any unreacted zinc. Fine, white crystals separated as the filtrate cooled. The product did not melt below 300° C. When ignited, it charred with very little burning, and, on further ignition, a pale yellow residue was left. A solution of this residue gave a well defined qualitative test for zinc. The compound was recrystallized from 6 N hydrochloric acid. With slow cooling, the product crystallized in long, white rods, some crystals being three inches long. Before analysis, the product was dried at 120° C. for seven hours. The compound was analyzed for chlorine and nitrogen. The analyses and qualitative test for zinc formed the basis for the assigned formula. Data for this compound are listed in Table II.

(26) 1,4-Piperazinium di-stearate

$$CH_3(CH_2)_{16}COOH \cdot HNC_4H_8NH \cdot HOOC(CH_2)_{16}CH_3$$

Ten grams of piperazine hexahydrate and 16.7 g. stearic acid were dissolved in separate portions of 95% alcohol. The piperazine solution was poured into the stearic acid solution with stirring. No reaction could be perceived for about two or three minutes. After that, white crystals began forming, finally resulting in a thick mass. After standing overnight, the mixture was filtered and the product washed with ether. The compound was recrystallized twice from 95% alcohol and dried over P_2O_5 for several weeks prior to analysis. Its composition was determined by a Kjeldahl analysis for nitrogen and by a combustion furnace analysis for carbon and hydrogen. Analyses, properties etc. are recorded in Table II.

(27) 1,4-Piperazinium di-palmitate

$$CH_3(CH_2)_{14}COOH \cdot HNC_4H_8NH \cdot HOOC(CH_2)_{14}CH_3$$

Twenty-six and four tenths grams of palmitic acid was dissolved in 400 cc. warm 95% alcohol. Ten grams of piperazine hexahydrate was dissolved in 200 cc. 95%

alcohol. These solutions were mixed and stirred one and one-half hours. A white precipitate started forming within about thirty minutes after the solutions were mixed. The product was recrystallized twice from 95% alcohol and dried in a desiccator over P_2O_5. A nitrogen analysis by the Kjeldahl method and a carbon and hydrogen analysis by the combustion furnace method determined the composition of the salt. Data for this compound are recorded in Table II.

SUMMARY

A study of the condensation of aldehydes with piperazine and N-monophenylpiperazine in neutral solution and in the presence of reducing agents has been made.

The contradictory reports in the literature on the condensation of piperazine and aldehydes were investigated. In all cases of condensation using piperazine, water was split out between two amino groups and one carbonyl group, giving a compound of the N,N′-bis-piperazyl alkyl methane type. Using N-monophenylpiperazine, condensation took place in an analogous manner, yielding compounds of the N,N′-bis(phenyl piperazyl) alkyl methane type.

Satisfactory methods have been derived for the preparation of alkyl piperazines by the condensation of piperazine or N-monophenylpiperazine with aldehydes in the presence of a reducing agent. Zinc and hydrochloric acid was used as the reducing agent for those aldehydes which are soluble in water. Formic acid was used as the reducing agent for those aldehydes which are insoluble. These methods gave very good yields and the compounds were quite easy to purify.

A double salt of piperazine and zinc chloride has been prepared.

Two salts of piperazine have been prepared. These salts consist of high molecular weight aliphatic acids.

In the course of this investigation, fourteen new compounds were prepared. Several other compounds were prepared and their structures and properties investigated.

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BIOGRAPHY

W. T. Forsee, Jr. was born March 14, 1909 at Owenton, Kentucky. He attended Georgetown College, Georgetown, Kentucky, and graduated with the degree of Bachelor of Arts (Magna cum Laude) in 1931. He attended the Graduate School of the University of Kentucky during the second semester of the 1930 - 31 session. He attended the University of Florida from 1931 to 1935, obtaining the degree of Master of Science in chemistry in August 1932. He was a laboratory assistant in the chemistry department of Georgetown College from 1929 to 1931 and was a graduate assistant in the chemistry department of the University of Florida from 1931 to 1935. He is a member of Gamma Sigma Epsilon and Alpha Chi Sigma, national honorary chemical fraternities, Phi Kappa Phi, a national scholastic fraternity, and The American Chemical Society.

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee, and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

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James N. Anderson
Dean

Supervisory Committee:

C.B. Pollard.
Chairman

T.M. Ellis.

Townes R. Leigh

R.C. Williamson

A.A. Bless.